# PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>APM/6978-WO | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No.<br>PCT/GB 03/02369 | International filing date *(day/month/year)*<br>30.05.2003 | Priority date *(day/month/year)*<br>31.05.2002 |
| International Patent Classification (IPC) or both national classification and IPC<br>C12Q1/68 | | |
| Applicant<br>IMMUNOCLIN LIMITED | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 29.12.2003 | 23.06.2004 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Trommsdorff, M<br>Telephone No. +49 89 2399-7361 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/02369

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-44 as originally filed

**Claims, Numbers**

1-17 received on 07.06.2004 with letter of 03.06.2004

**Drawings, Sheets**

1-3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-10, 12, 13 (all partly)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-10, 12, 13 (all partly)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-17 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-17 |
| Industrial applicability (IA) | Yes: | Claims | 1-4, 11, 14-17 |
| | No: | Claims | 5-10, 12, 13: no opinion |

2. Citations and explanations

   **see separate sheet**

## 1. Cited documents

D1: LIO D ET AL: 'Interleukin-10 promoter polymorphism in sporadic Alzheimer's disease.' GENES AND IMMUNITY, vol. 4, no. 3, April 2003 (2003-04), p.234-8,ISSN: 1466-4879 (ISSN print)

D2: REMARQUE E J ET AL: 'Patients with Alzheimer's disease display a pro-inflammatory phenotype' EXPERIMENTAL GERONTOLOGY, vol. 36, no. 1, January 2001 (2001-01), p.171-6, ISSN: 0531-5565

D3: TURNER D M ET AL: 'AN INVESTIGATION OF POLYMORPHISM IN THE INTERLEUKIN-10 GENE PROMOTER' EUROPEAN JOURNAL OF IMMUNOGENETICS, OXFORD, GB, vol. 24, no. 1, 1997, p. 1-8, ISSN: 0960-7420

D4: PAPASSOTIROPOULOS ANDREAS ET AL: 'Genetics of interleukin 6: Implications for Alzheimer's disease' NEUROBIOLOGY OF AGING, vol. 22, no. 6, November 2001 (2001-11), p. 863-71, ISSN: 0197-4580

D5: WO 95 33992 A (MOR RESEARCH APPLIC LTD ;UNIV BAR ILAN (IL); SHALIT FRANCES (IL)) 14 December 1995 (1995-12-14)

D6: MARTIN E R ET AL: 'SNPING AWAY AT COMPLEX DISEASES: ANALYSIS OF SINGLE-NUCLEOTIDE POLYMORPHISMS AROUND APOE IN ALZHEIMER DISEASE' AMERICAN JOURNAL OF HUMAN GENETICS, AMERICAN SOCIETY OF HUMAN GENETICS, CHICAGO, IL, US, vol. 67, August 2000 (2000-08), p.383-94, ISSN: 0002-9297

D7: DEPBOYLU CANDAN ET AL: 'Lack of association of interleukin-10 promoter region polymorphisms with Alzheimer's disease.' NEUROSCIENCE LETTERS, vol. 342, no. 1-2, 15 May 2003 (2003-05-15), p.132-4, ISSN: 0304-3940 (ISSN print)

## 2. Re Item III

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

2.1. Claims 5-10 and 12, 13 (as far as in vivo methods are concerned) relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

3. Re Item V

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Since the priority document has not been furnished yet, the examining division considers the priority to be valid for the time being. Thus, intermediate document D1 will not be considered as prior art document.

3.1. Claim 1 relates to a method of diagnosis of a predisposition to Alzheimer disease (AD) by determining the allelic variants of IL-10.
Since none of the prior art documents discloses such a method, the claims are novel (Art. 33(2) PCT).

D2 analyses the levels of IL-1beta, IL-6 and IL-10 in AD patients compared to controls and shows that IL-1beta and IL-6 levels are 2-3-fold higher, whereas IL-10 levels are 2 to 4-fold lower in blood samples of AD patients (Table 1).
D2 suggests that the cytokine levels can be used to predict a risk of AD (last paragraph).
The difference between D2 and claim 1 resides in the method for assessing the AD risk: in D2 the protein levels of IL-10 are measured, whereas in claim 1 the gene polymorphisms in the promoter region of IL-10 are analysed.

D3 identifies 3 single base pair substitutions (at positions -1082, -819, -592, respectively) in the IL-10 gene promoter and shows that the polymorphism in position -1082 correlates with IL-10 production in vitro.
In the light of D3 it would have been obvious to the skilled person that since the IL-10 protein levels are associated to specific IL-10 allelic variants in the promoter region, the analysis of said variants can also be used as a basis for determining the risk of AD.
Thus, the claimed subject-matter lacks an inventive step (Art. 33(3) PCT).

3.2. It should further be noted that several other documents teach a correlation between cytokine levels and the risk of AD.
D4, for example, reviews different data on IL-6 and shows that there exists a correlation between IL-6 levels and AD.

D5 analyses different cytokine levels in AD patients compared to controls and shows that levels of IL-2, IFN-gamma, TNF-alpha and IL-6 are significantly increased in AD patients in the moderately-severe stage of the disease (see examples).
There are however also contradictory results on the association between IL-10 and the risk for AD, as shown by the later published document D7.

3.3. Although the claims are broadly directed to a multitude of cytokines, the description only shows data for certain cytokines. A correlation with AD is actually only shown for IL-6 and IL-10. Thus, the claims should be restricted to those cytokines for which an effect was shown (Art. 6 PCT).

3.4. The subject-matter of claims 1-4 and 11-17 is industrially applicable in the field of pharmaceutical industry (Art. 33(4) PCT).